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Terawatt (TW) lasers have become commonplace since the development of the chirped-pulse amplification method using Ti:sapphire and Nd:glass laser rods. We have measured the minimum visible lesion (MVL) thresholds for porcine1 (Yucatan minipig) skin using TW laser pulses.
Our system produced laser pulses at 810 nm and sub-50 femtoseconds. These 1–2 TW laser pulses created multiple self-focusing (SF) filaments during propagation and were directed on the flanks of mini-pigs under anesthesia. We measured the pulse energies necessary to determine the ED50 skin damage thresholds.

15. SUBJECT TERMS
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ED_{50} Study of Femtosecond Terawatt Laser Pulses on Porcine Skin

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Background and Objectives:: Terawatt (TW) lasers have become commonplace since the development of the chirped-pulse amplification method using Ti:sapphire and Nd:glass laser rods. We have measured the minimum visible lesion (MVL) thresholds for porcine[1] (Yucatan mini-pig) skin using TW laser pulses.

Study Design/Materials and Methods:: Our system produced laser pulses at 810 nm and sub-50 femtoseconds. These 1–2 TW laser pulses created multiple self-focusing (SF) filaments during propagation and were directed on the flanks of mini-pigs under anesthesia. We measured the pulse energies necessary to determine the ED_{50} skin damage thresholds.

Results:: The MVL ED_{50} threshold at 1 hour was 8 mJ and increased to 21 mJ after 24 hours. Histological sections were obtained after 1-hour and 24-hour readings.

Conclusions:: The damage patterns on the skin indicated the number of filaments in the laser pulse. Many of the pulses produced only superficial damage that disappeared in 24 hours and that nearly three times the pulse energy was required to cause subdural or cellular damage. With further research, non-thermal tissue ablation using TW laser pulses could provide a viable alternative to current techniques of laser use in dermatology. Lasers Surg. Med. 37:59–63, 2005. © 2005 Wiley-Liss, Inc.

Key words: infrared; mini-pig; MVL; ablation; dermatology; laser induced breakdown

INTRODUCTION

Terawatt (TW) lasers have become commonplace since the development of the chirped-pulse amplification method using Ti:sapphire (titanium-doped sapphire) and Nd:glass (neodymium-doped glass) laser rods. Generating pulses with 1–2 TWs of peak power at 810-nm wavelengths and 40-femtosecond pulse duration (40–80 mJ pulse energies) at pulse repetition rates of 10 pps has become easier to do. However, the proliferation of table-top TW laser systems has introduced many new hazards to researchers and the general public because these high intensity pulses propagate through the atmosphere differently than those with longer pulse durations. These ultrashort, TW pulses can propagate over long distances in various media without losing large amounts of energy, as long as the pulse power is greater than the critical power ($P_c \sim 3$ GW) for self-focusing (SF). These pulses form multiple, stable light filaments (approximately 100 μm in diameter) propagating for tens of meters through the atmosphere and are repeatable from pulse to pulse in their pattern formation. These filamentations can be dynamically guided over long distances [1]. SF produces these filaments and increases their irradiances high enough to permit multiphoton ionization. This multiphoton ionization generates low-density plasmas (LDPs) as the pulse propagates through the atmosphere that have valuable properties for many other applications (including LIBS, LIDAR, arc discharges, etc.). White-light continuum or super-continuum (SC) can be produced by self-phase modulation as the pulse propagates through the air. Another contributing factor to SC is the rapid variation of index of refraction of air from the front to the back of the high intensity laser pulse. When the laser wavelength is in near infrared, the generation of optical frequencies can be quite broad; it can reach from the UV to the far infrared range. While SF is responsible for the filamentation, it is balanced by diffraction of the laser beam and refraction from the plasma. Thus, there is a dynamic balance between Kerr SF and self-defocusing by multiphoton ionization of the air molecules.

[1]The animals involved in this study were procured, maintained, and used in accordance with the Federal Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources—National Research Council. Brooks City-Base, TX has been fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) since 1967.

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the United States.

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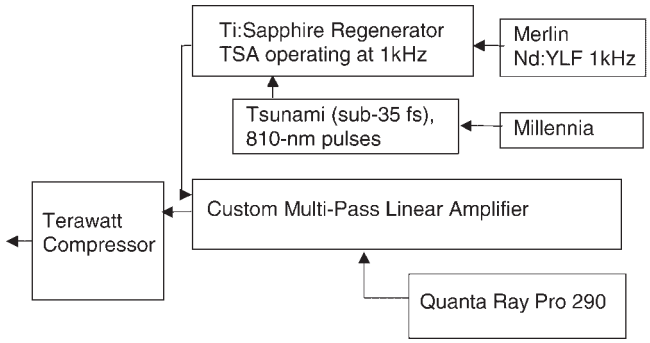
In this study, we have concentrated on skin effects because of the lack of data that have been previously reported supporting the current ANSI-Z136.1-2000 [2] standard for the maximum permissible exposure (MPE) levels. We have previously reported the effects of these ultrashort laser pulses in live eyes [3] from measurements taken using 44-femtosecond pulses at 810 nm to determine the MVL-ED_{50} thresholds. These thresholds were measured with and without pulse-chirping to counter the effects of group velocity dispersion (GVD). We also compared these eye MVL thresholds to the laser-induced breakdown (LIB) and LDP thresholds measured in an artificial eye. GVD plays a much larger role in the eye than when propagating in the atmosphere because the nonlinear index of refraction is so much larger in the eye or in aqueous media than in air. There are no skin-MPE levels for pulse durations shorter than a nanosecond in the current ANSI standard, and only a few experimental data points have been reported in the literature. None have been reported for these TW laser pulses with multiple filaments or given the MVL-ED_{50} thresholds.

The Yucatan mini-pigs were used as animal subjects in this study. The Yucatan mini pig has skin on the flank with more human-like characteristics in comparison to the Yorkshire pig or other animal species [4]. We have previously reported on the skin effect of near-infrared laser pulses operating at 1.314 [5] and 1.54 nm [6] with longer pulse durations (0.6, 0.35 microseconds, and 50 nanoseconds). In these studies, we measured the MVL thresholds as a function of laser spot size on the skin and pulse duration, and determined the spot-size dependency for each wavelength. We also modeled the skin exposures using a thermal model developed in our laboratory [7] and compared the results of the model with ANSI standards for long pulse durations. However, the model used in these experiments is not capable of any temperature or damage predictions using these sub-50-femtoseconds pulses and no previous model predictions are available.

MATERIALS AND METHODS

Our experimental setup consisted of a Ti:Sapphire chirped-pulse amplification system (Graph 1). The 810 nm, sub-45-femtoseconds pulses were produced by a Tsunami model 3941-35FS laser system. These pulses were then stretched and amplified by a Ti:sapphire regenerative amplifier (modified TSA, operating at 1 kHz). The regenerative amplifier was optically pumped by a kHz class Nd:YLF frequency-doubled (1054–527 nm) laser. In the regenerative amplifier, the pulse was amplified by nearly a factor of a million (nJ to mJ). Consequently, a single mJ pulse was gated out of the regenerative amplifier and sent to a custom-made, four-pass amplifier (TW amplifier system). The TW amplifier system was designed to increase the TSA regenerative-amplifier pulse energy from 1 mJ to about 100 mJ when the amplifier is pumped by a Q-switched Nd:YAG laser operating at about 600 mJ at 532 nm.

The beam leaving the compressor was then down-collimated using a telescope system consisting of −2.0 m and +1.0 m radius of curvature mirrors. The beam generally produced several filaments (up to 12 depending on energy) propagating for approximately 10–15 m through the atmosphere. The threshold energy for the filament formation was 8 mJ. The theoretical diameter of a single filament is approximately is 100 μ [8].



Graph 1. Experimental setup.

EXPERIMENTAL PROCEDURES

Three female Yucatan mini-pigs (Lonestar Laboratory Swine, Seguin, TX), weighing between 15 and 20 kg, were involved in this study. All three animals were between 3 and 8 months of age. The study fell under the animal use protocol titled "Evaluation of Laser induced Corneal Lesions in the Dutch Belted Rabbit and Skin Lesions in the Yucatan Mini-Pig," which was approved by the Brooks City-Base, TX Institutional Animal Care and Use Committee (IACUC). None of the animals were euthanized after exposure or biopsy, since they were part of an animal-sharing program. Pigs were fed standard, commercially available diets, and had unlimited access to water. However, all solid food was withheld for 12 hours prior to laser exposure and biopsy collection. The animals involved in this study were procured, maintained, and used in accordance with the Federal Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources—National Research Council. Brooks City-Base, TX has been fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) since 1967.

Subjects were received from an attendant veterinary technician via stretcher, sedated with indwelling, intravenous catheter placed in an ear vein, and intubated prior to arrival at the laboratory. The pigs were sedated by single syringe injection of Tiletamine/Zolazepam (4–6 mg/kg) intramuscular (IM) and Xylazine (2.2 mg/kg) IM, and were maintained on inhalation isoflurane anesthesia during all procedures. After sedation, hair on the flank was clipped using electric hand clippers, and the cleansed skin was inspected by each of three evaluators to check for redness, irritation, or other confounding marks. Physiological parameters were monitored throughout all procedures, and all subjects were kept warm during the entirety of the

procedures. Three 5-mm punch biopsies were obtained from each subject immediately after the 1-hour postexposure reading and three more after the 24-hour postexposure reading. One of the three biopsy sites on each animal was chosen as a control (taken from a location above the grid, where there was no laser exposure). Harvested tissue was prepared for histopathologic analysis using 10% formalin solution, then blocked in paraffin and stained with hematoxylin/eosin. H&EBuprenorphine (0.05–0.1 mg/kg) was administered intramuscularly for analgesia after biopsies were complete. All biopsy sites were closed with non-absorbable 2–0 sutures and topically medicated with Trio-mycin ointment for infection prophylaxis. The animals were returned to their runs upon recovery to sternal recumbency from anesthesia.

Target areas were marked with a 5×11 grid or a 6×10 grid using a permanent-ink marker, making a total of 55 or 60 grid squares per flank. The pig was positioned at a distance of 3 m from the laser system in an upright position so that the flank could be exposed to the propagating beam. The animal-positioning stage was adjusted horizontally and vertically to locate exposures in each of the grid positions. Pulse energies were delivered to each grid site at systematically varied intensities.

Visual evaluation of skin exposure sites was performed immediately after exposures of a grid. Three trained lesion readers were used to evaluate the presence or absence of skin lesions. A lesion is defined as a visible change in the skin at the exposure site. It could be a discoloration, redness, and/or removal of the outer skin layer. The readers used a lighted magnifying glass to examine the exposed skin area. The three readers independently examined the flank lesions immediately after all exposures were accomplished. A lesion was recorded as a "yes" if at least two readers identified it as positive. The exposure grids were re-examined in the same way at 1-hour and at 24-hour postexposure.

Probit [9] analysis was the statistical method used to determine the estimated dose for 50% probability of laser-induced damage (ED_{50}) for the in-vivo skin model. Reading of injured sites were performed acutely (10-minute post-exposure), at one hour and at 24-hour postexposure. All data points were entered into the probit statistical analysis package and the ED_{50}s were calculated along with their fiducial limits (FLs) at the 95% confidence level. The slope of the probit curve at the ED_{50} value was also calculated together with probabilities from 1% to 99% levels.

RESULTS

Results of the MVL-skin damage threshold measurements are given in Table 1 for single 44-femtosecond, 810-nm, TW pulses for both the 1-hour reading and the 24-hour postexposure reading together with their FL calculated at the 95% confidence level. Also the slope of the probit curve at the 50% probability for the 24-hour reading is shown in the last column together with the number of exposures. For this pulse duration and wavelength, the 1-hour ED_{50} threshold is much lower than the 24-hour reading. The FLs calculated for all ED_{50} thresholds at both the 1-hour and 24-hour times were within $\pm 17\%$ of the ED_{50} value. As shown in Table 1, the 24-hours reading is 2 1/2 times larger than the 1-hour reading.

Photographs were taken prior to exposures, at the 1-hour reading and again after 24 hours to document the appearance of the lesions. Figure 1 shows the appearances of the lesions at the 1-hour postexposure reading and Figure 2 shows magnified images of two of the lesion sites. Figure 1 clearly shows the grid pattern on the skin and each lesion near the center of each square. It is to be noted that there are numerous small, white spots in the skin showing the pattern of the filamentation of the laser beam as it propagated from the laser to the pigskin. Several of the high-energy pulses produced at least five filaments, creating burn spots in the skin and in one case, seven filaments could be counted in the photo. For most of these high-energy pulses, energies greater than 25 mJ, a flash of light could be seen and a pop heard with the breakdown of the air at the surface of the skin. Figure 3 was taken at the 24-hours postexposure and shows much fewer lesions discernable than in Figure 1. Figure 3 shows the skin after 24 hours in which the animal was allowed to roam freely in its pen. The three puncture wounds with sutures were from the biopsy samples taken 1-hour postexposure. It is obvious that many of the damage sites were obscured by the animal rubbing against the walls, floor, etc. Even the grid pattern was much less distinctive. Many of the lesions observed at the 1-hour reading were not discernable after 24 hours for reasons stated above. This could explain some of the large differences between the 1-hour and 24-hour readings and the ED_{50} values shown in Table 1.

HISTOLOGICAL RESULTS

Histologic evaluation of the skin biopsies demonstrated essentially normal tissue at the 1-hour sample, with the exception of skin biopsy (Figure 4), which received a 12.1-mJ exposure. The lesion in this biopsy was consistent with a partial thickness burn, characterized by coagulative necrosis of the epithelium and superficial dermis. The depth of the dermal necrosis was approximately 1/3 the total depth of the dermis. The necrotic change in the superficial dermis was composed of a wedge-shaped mass of amorphous coagulated material exhibiting bright eosinophilic staining

TABLE 1. Visible Lesion Thresholds in Porcine Skin From a Terawatt (TW) Laser

TW laser subjects, parameters	MVL-ED_{50} 1-HR reading	MVL-ED_{50} 24-HR reading	Slope of probit at 24-hours
Three subjects, three flanks	Energy in mJ	Energy in mJ	δprob/δdose
810-nm, 44-Femtosecond	8.2 (9.5–6.7)	21.3 (24.6–18.2)	3.9
170 exposures	Prob.$\chi = 1.0$	Prob.$\chi = 0.9$	

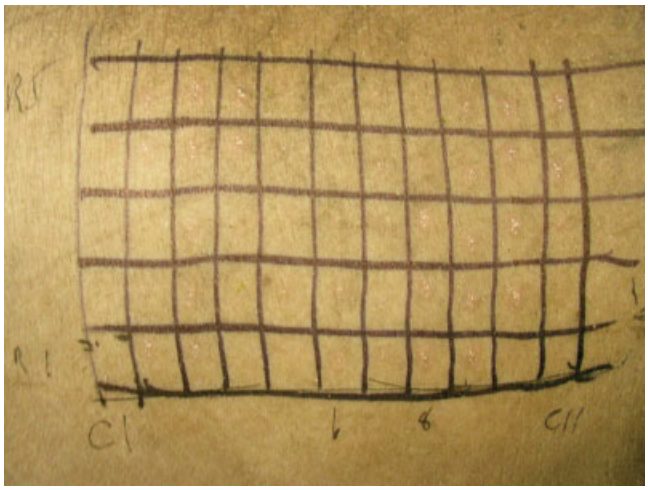


Fig. 1. Picture of the grid pattern and lesions at 1-hour postexposure. The grid size is approximately 1 cm.

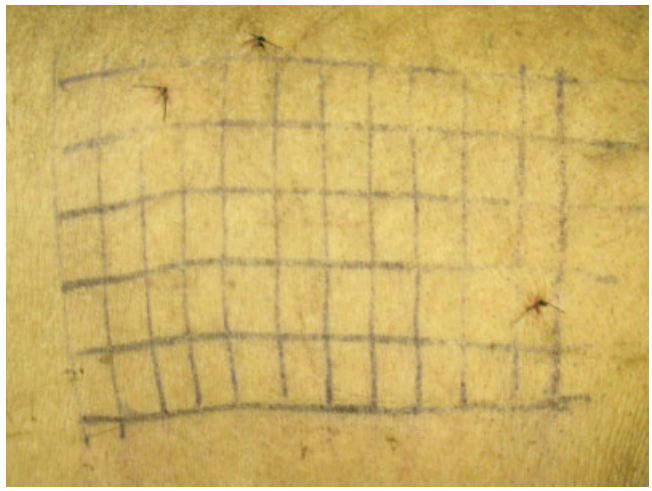


Fig. 3. Photo of grid pattern after 24-hour postexposure showing fewer lesions.

and loss of cellular detail with maintenance of overall architecture. The point was measured at the deepest margin of thermal injury associated with immediate necrosis and collagen degeneration.

All samples taken at 24 hours exhibited focal to focally extensive coagulative necrosis of the epithelium, often with attendant neutrophilic and eosinophilic inflammation and congestion of the superficial dermal vascular plexus, which would eventually lead to the loss of those layers. There was occasional clefting at the dermal epidermal junction with vacuolation of the basal epithelial cells. The change in the epithelium consisted of a well-demarcated, brightly eosinophilic area of necrosis, with loss of cellular detail, consistent with a first-degree thermal injury.

DISCUSSION

Visible lesion thresholds were determined at both 1 hour and 24 hour postexposure as listed in Table 1. These threshold-ED_{50} values show that many of the lesions observed at 1 hour simply disappeared during the next 24 hours. 10 minutes postexposure, most of the exposure sites showed erythema (a blotchy red rash) in the skin. Most of this erythema disappeared during the first hour before the 1-hour reading and by 24 hours, most all had disappeared. Many of the lesions observed at the 1-hour reading appeared to be surface damage only, but were counted as observable lesions for the probit analysis. Lesions observed at 24 hours showed damage below the skin surface as described in the histology above. Thus, the ED_{50} threshold did produce damage that was considered to be 1st-degree thermal injury. This is consistent with the safety standards being based on the 24-hour damage thresholds and not the 1-hour threshold.

The higher pulse energies used in this study generated strong LIB at the surface of the skin and whitening of the

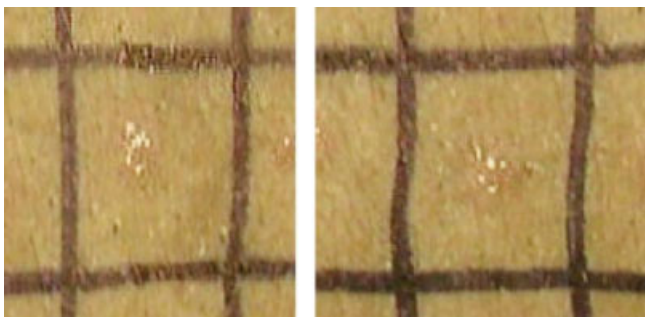


Fig. 2. Magnified images of two lesions observable in Fig. 1 showing the filament pattern.

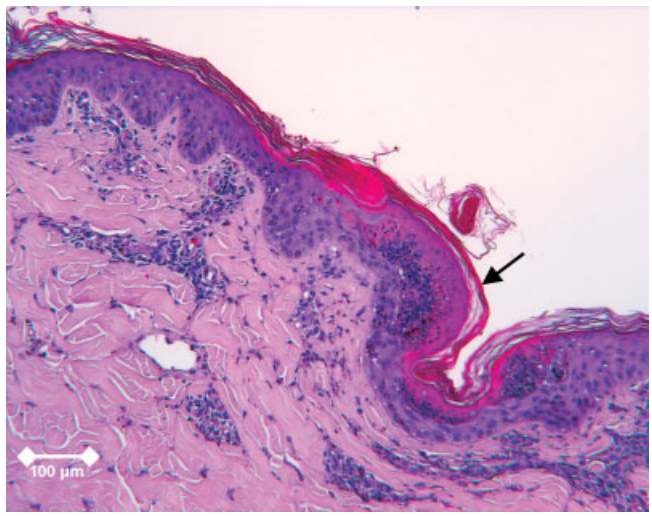


Fig. 4. Dermis and epidermis; porcine, 12 mJ exposure. The arrow points to focally extensive area of coagulative necrosis of the superficial dermis with cellular infiltrate and vacuolar change. There is increased cellularity surrounding all subjacent dermal vascular plexus.

outer layers was clearly evident, which we believe indicated ablation. The intention of this study was not to measure any ablation effects or rates, but we may compare our MVL-thresholds energies to threshold energies for tissue ablation reported by other researchers for these femtosecond pulses [10–12].

Watanabe et al. [10], reported their study on black and albino guinea pig skin for femtosecond laser pulses. They performed threshold measurements using red, visible laser pulses at 65 femtosecond, generated by a tunable dye laser. They determined threshold doses required for rupturing melanosomes in the pigmented skin for pulse durations from 65 femtoseconds to 35 nanoseconds. They reported that at and above 0.31 J/cm^2, melanosome disruptions occurred. Also at 0.92 J/cm^2, increased cytoplasmic vacuolizations were noted. For a 1 cm^2 spot size on the skin and at an ED_{50} of 21 mJ, the threshold was found to be 0.02 J/cm^2 for damage. In this study, the laser pulse duration was about 45 femtoseconds and laser pulse energy was about 65 mJ. For the energy and pulse duration stated, multiple filaments were observed in the atmosphere. The very low threshold can be explained by the fact that there exist much higher irradiance levels inside these filaments causing the damage.

Another research group, Frederickson et al. [11], reported ablation thresholds using Ti:sapphire system (the same type lasers as our system) on Sprague-Dawley female rats. Their pulse durations were less than 120 femtoseconds. They found the ablation threshold to be 2 mJ corresponding to an irradiance of 2.5 TW/cm^2 for an average spot size on the skin of 1 mm in diameter. They also found that only one pulse was required to ablate epidermis at 22 mJ/pulse, whereas at energies of 9.0 mJ/pulse 10 pulses were required, and at energies of 2.0 mJ/pulse 100 pulses were required. A third study, by Puliafito et al.[12], reported a corneal ablation threshold of 2.5 μJ at 100 femtoseconds at wavelength of 625 nm. Puliafito et al., focused the beam to a minimum possible diameter. For their thresholds to be equivalent to Frederickson et al., a calculation would estimate the beam diameter to be 35 μm.

CONCLUSIONS

The results presented herein represents the first known porcine skin effects from TW lasers operating in the near-IR and these data should be added to the data-bank used in setting MPE limits proposed by safety standards committees. Since safety standards are generally developed on published research, these data will support future standards. The MVL ED_{50} threshold of 8 mJ at 1 hour is near the ablation threshold energy, which produced acute erythema resulting from acoustic damage. The erythema resolved before the next evaluation. The 24-hour threshold energy was 21 mJ; almost three times the 1-hour threshold. These lesions had a different appearance from lesions evaluated after 1 hour. Histologic damage was not evident below the epidermis. We observed that all lesions indicated at the 24-hour read were accompanied by plasma similar to the results reported by Frederickson et al. [11].

Femtosecond, TW laser-induced plasma formation provides tissue ablation which is different than thermal destruction of tissue by conventional lasers. Our experiment showed that photodistruption via non-linear femtosecond pulse propagation and optical breakdown are possible in porcine skin at relatively low pulse energies. Femtosecond, TW lasers could provide alternatives to conventional lasers when intended use is the precise removal of tissue.

The data presented here are part of our ongoing research of ultrashort pulsed laser bioeffects using TW-class lasers. It is too early to make specific recommendations as to medical use or use in establishing safety standards.

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